REMARKS

Please reconsider the application in view of the above amendments and the following remarks. Applicant thanks the Examiner for carefully considering this application.

Disposition of Claims

Claims 1-5, 7, 9-15, and 19-21 were pending in this application. Claims 2-21 are cancelled, and claims 22-24 are added by this reply. Therefore, claims 1 and 22-24 are pending in this application. Claims 1 and 23 are independent. The remaining claims depend, directly or indirectly, from claims 1 and 23.

Objection(s)

1. Claims 8 and 16-18 were objected to as including incorrect status identifiers. These claims have been cancelled, rendering this objection moot.
2. The previously submitted amended specification and abstract were objected to as including new matter, i.e., "DNA immobilizing-agent coating" and "biomolecule-immobilizing agent coating." The specification and abstract have been amended to remove these terms. Accordingly, withdrawal of this objection is respectfully requested.

Rejection(s) under 35 U.S.C § 112

Claims 1-5, 7, 9-15, and 19-21 stand rejected under 35 U.S.C. § 112 as failing to comply with the written description requirement. Claims 2-5, 7, 9-15, and 19-21 have been cancelled, rendering this rejection moot. Claim 1 has been amended in this reply to remove the phrase, "biomolecule-immobilizing agent coating," which was objected to as including new matter. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1-5, 7, 9-15, and 19-21 stand rejected under 35 U.S.C. § 112 as being indefinite. Claims 2-5, 7, 9-15, and 19-21 have been cancelled, rendering this rejection moot. Claim 1 has been amended in this reply to clarify the recited invention. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 5, 19, and 20 were rejected under 35 U.S.C. § 112 as being indefinite for

including improper Markush format. These claims have been cancelled, rendering this rejection moot. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection(s) under 35 U.S.C § 102

A. Claims 1-5, 7, 9-15, and 19-20 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Dale (U.S. Patent No. 6,440,723). Claims 2-5, 7, 9-15, and 19-20 have been cancelled, rendering this rejection moot. Claim 1 has been amended in this reply to clarify the recited invention. To the extent that this rejection may still applied to the amended claim 1, it is respectfully traversed.

Two approaches are known in the prior art for the preparation of DNA microarrays: photolithography and spotting. Photolithography provides DNA detection points that are very small and uniform, but tend to be very expensive. Spotting methods are cost effective, but tend to lack uniformity and precision. Embodiments of the invention have the advantages of both the spotting methods (low cost) and the photolithography method (small size, precision, and uniformity). (Specification, p. 3, line 10 – p. 4, line 17).

According to one embodiment of the invention, photolithography is used to produce specific attachment spots on a microarray support. (FIG. 1) These spots are small and uniform in size – owing to the photolithographic method. Biotin-containing molecules are then linked to the specific attachment spots, forming a layer of biotin at the attachment spots. Then, a solution containing avidin or streptavidin is applied to the biotin layer that have been attached to the specific spots on the support. Avidin or streptavidin molecules are retained by the tight avidin-biotin interactions to form a biomolecule microarray support, as recited in claim 1. (FIG. 2).

Because each avidin/streptavidin molecule has multiple biotin binding sites, the avidin or streptavidin molecules on the support retain the ability to bind other biotin-containing probe molecules (e.g., biotinylated probe DNA 21 in FIG. 3). Thus, a support in accordance with embodiments of the invention (such as that recited in claim 1) can be used to generate various microarrays (e.g., DNA microarrays, RNA microarrays, or protein microarrays), by using different biotinylated probe biomolecules (e.g., biotinylated-DNA, biotinylated-RNA or biotinylated-protein).

Because the biomolecule-attachable spots of the microarray support of claim 1 have a

very high uniformity of shape and size (which are determined by photolithography), the number of biotin molecules bound to each biomolecule-attachable spot is substantially the same. Therefore, the number of avidin or streptavidin molecules bound to the biotin molecules on each spot is also substantially identical.

The idea of attaching an equal number of biomolecule-binding molecules (e.g., avidin or streptavidin) on all spots to make quantitative analysis possible by first forming attachment spots highly uniform in shape and size, then forming a layer of small molecule anchor followed by a layer of large-molecule probe binding sites is not disclosed in the prior art. With the approach disclosed in this invention, possible variations in the numbers of molecules which bind to the spots can be eliminated or minimized by allowing a layer of larger molecules (avidin or streptavidin, much larger in molecular size than biotin) to bind to a layer of smaller molecules (biotin, much smaller in molecular size than avidin or streptavidin) attached to the surface of the support.

Due to the tight binding between avidin and biotin, the binding reaction (illustrated in FIG. 2) will always reach completion. Thus, if the probe biomolecule (e.g., biotinylated-DNA) is applied in excess, the amount of the probe biomolecule bound is only determined by the amount of avidin (or streptavidin) in each attachment spot. The amount is avidin in each spot is uniform, owing to the precision of the photolithography. Consequently, as long as the amount of probe biomolecule is in excess, any variation in the volumes or concentrations of the probe biomolecule in the spotting step will not affect the amount of probe biomolecule bound in the microarray. Claims 23 and 24 recite embodiments that specifically require the application of at least 3×10^9 probe biomolecules to each spot.

As amended, claim 1 recites the limitations of "the probe biomolecule attachable spots have a layer of biotin formed on the surface of the support and a layer of avidin or streptavidin bound to the layer of biotin" and "the probe biomolecule-attachable spots have a uniform shape and size determined by photolithograph, equal to or smaller than 200 μm." The biomolecule-attachable spots of the microarray support of claim 1 have a very high uniformity of shape and size with a degree of accuracy achievable only by photolithography. The uniform size (no more than 200 μm) and shape of these spots are not achievable with the spotting techniques of Dale, Brown et al., and Sluka et al.

Specifically, Dale uses a conventional spotting technique, which cannot provide small

(no more than 200 μm) and uniform attachment spots. In addition, Dale discloses an array with modified oligonucleotide compositions (probe biomolecules) already associated with distinct areas on the surface of a support. In contrast, the microarray support recited in claim 1 is a general support that can be used to bind any biotinylated probe molecules to form the desired microarrays. More importantly, Dale fails to teach or suggest the limitations recited in claim 1, i.e., "the probe biomolecule attachable spots have a layer of biotin formed on the surface of the support and a layer of avidin or streptavidin bound to the layer of biotin" and "the probe biomolecule-attachable spots have a uniform shape and size determined by photolithograph, equal to or smaller than 200 μm."

In view of the above, claim 1 as amended is patentable over Dale. Dependent claim 22 is allowable for at least the same reasons. Accordingly, withdrawal of this rejection is respectfully requested.

B. Claims 1-3, 5, 9, 12, 13, and 19 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Brown et al. (U.S. Patent No. 5,807,522). Claims 2-3, 5, 9, and 12-13 have been cancelled, rendering this rejection moot. Claim 1 has been amended in this reply to clarify the recited invention. To the extent that this rejection may still applied to the amended claim 1, it is respectfully traversed.

As noted above, claim 1 recites the limitations of "the probe biomolecule attachable spots have a layer of biotin formed on the surface of the support and a layer of avidin or streptavidin bound to the layer of biotin" and "the probe biomolecule-attachable spots have a uniform shape and size determined by photolithograph, equal to or smaller than 200 μm." The biomolecule-attachable spots of the microarray support of claim 1 have a very high uniformity of shape and size with a degree of accuracy achievable only by photolithography.

Because Brown et al. fail to disclose or suggest these limitations, claim 1 as amended is patentable over Brown et al. Dependent claim 22 is allowable for at least the same reasons. Accordingly, withdrawal of this rejection is respectfully requested.

C. Claims 1-3 and 9 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Sluka et al. (U.S. Patent No. 6,221,674). Claims 2-3 and 9 have been cancelled, rendering this

rejection moot. Claim 1 has been amended in this reply to clarify the recited invention. To the extent that this rejection may still applied to the amended claim 1, it is respectfully traversed.

As noted above, claim 1 recites the limitations of "the probe biomolecule attachable spots have a layer of biotin formed on the surface of the support and a layer of avidin or streptavidin bound to the layer of biotin" and "the probe biomolecule-attachable spots have a uniform shape and size determined by photolithograph, equal to or smaller than 200 μm." The biomolecule-attachable spots of the microarray support of claim 1 have a very high uniformity of shape and size with a degree of accuracy achievable only by photolithography. More importantly, the amended claim 1 recites a support having a layer of biotin and a layer of avidin or streptavidin ready to bind other biotinylated probe biomolecules.

Because Sluka et al. fail to disclose or suggest these limitations, claim 1 as amended is patentable over Sluka et al. Dependent claim 22 is allowable for at least the same reasons. Accordingly, withdrawal of this rejection is respectfully requested.

D. Claims 1-5, 7, 9-15 and 19-20 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Barrett et al (U.S. Patent No. 5,252,743). Claims 2-5, 7, 9-15 and 19-20 have been cancelled, rendering this rejection moot. Claim 1 has been amended in this reply to clarify the recited invention. To the extent that this rejection may still applied to the amended claim 1, it is respectfully traversed.

As noted above, claim 1 recites the limitations of "the probe biomolecule attachable spots have a layer of biotin formed on the surface of the support and a layer of avidin or streptavidin bound to the layer of biotin" and "the probe biomolecule-attachable spots have a uniform shape and size determined by photolithograph, equal to or smaller than 200 μm." The biomolecule-attachable spots of the microarray support of claim 1 have a very high uniformity of shape and size with a degree of accuracy achievable only by photolithography.

Barrette et al. discloses a microarray made by attaching a photoactivatable biotin derivative to the surface of a support, exposing the biotin derivative in a predefined region on the

surface by shining a light through a mask to form biotin, attaching avidin to the biotin, and immobilizing a biotinylated anti-ligand to the region, repeating the photoactivation of the biotin derivative in a predefined region and immobilization of an anti-ligand a necessary number of times. (Abstract; Column 5, line 59 - Column 6, line 17; Column 18, line 55 - Column 20, line 30; and Column 21, line 1 - 29).

Because the microarray of Barrette et al. has the remaining surface other than the detection spots coated with a photoactivatable biotin derivative, it must be stored with care because the biotin derivative on the surface can be activated if exposed to light during storage. Furthermore, the microarray of Barrette et al cannot be used with biomolecule probes, such as DNA probes, which are immobilized to the array using UV light because irradiation of UV light for immobilization of a biomolecule probe to the predefined region can remove the protecting groups of the biotin derivative on the other part of the surface.

In contrast, the surface other than the attachment spots of the biomolecule microarray support of claim 1 is exposed or covered with a cover coating. Therefore, the biomolecule microarray support of claim 1 does not need the greatest care for storage as required for the microarray of Barrette et al., and can be used for biomolecule probes such as DNA probes which are immobilized to the array using UV light. More importantly, Barrett et al. does not disclose the limitation of claim 1, i.e., "wherein the surface of the areas other than the spot areas is left exposed or covered with the cover coating."

Because Barrett et al. fails to disclose or suggest the limitations of claim 1, claim 1 as amended is patentable over Barrett et al. Dependent claim 22 is allowable for at least the same reasons. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection(s) under 35 U.S.C § 103

Claim 21 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Barrett et al. Claim 21 has been cancelled, rendering this rejection moot. Accordingly withdrawal of this rejection is respectfully requested.

New Claim

New claims 23 and 24 have similar limitations as those of claim 1. These new claims are patentable for at least the same reasons. In addition, new claims 23 and 24 recite the limitation

that the probe biomolecule-attacble spots have "a same amount of a probe biomolecule selected from the group consisting of DNA, RNA, PNA, and protein . . . by spotting equal to or greater than 3×10^9 probe biomoleucles on each of the spots."

It is known from measurement that if more than 3×10^9 probe biomolecules are spotted on each spot, the amounts of probe biomolecules immobilized on all spots are equal, as shown in Fig. 5. Therefore, quantitative analysis is made possible by the biomolecule microarray of claim 2. Biomolecule microarrays which can be used for quantitative analysis are not disclosed nor taught by the cited literature. Therefore, these new claims are petentable erences.

Conclusion

Claims 1 and 22-24 have been shown to be allowable over the prior art. The amendments are believed to require no further prior art search. Because the amendments simplify the issues for allowance or appeal, and do not constitute new matter, entry thereof is respectfully requested.

Applicant believes this reply is fully responsive to all outstanding issues and places this application in condition for allowance. If this belief is incorrect, or other issues arise, the Examiner is encouraged to contact the undersigned or his associates at the telephone number listed below. Please apply any charges not covered, or any credits, to Deposit Account 50-0591 (Reference Number 05426.014001).

Respectfully submitted,

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